Contovir – A New Adjuvant Therapy in Recurrent Respiratory Papillomatosis: A Case Study

Article · February 2016

DOI: 10.5812/ircmj.21577

9 authors, including:

Farzad Izadi
Iran University of Medical Sciences
39 PUBLICATIONS **52** CITATIONS
SEE PROFILE

Vita Derakhshandeh
Ahvaz Jondishapour University of Medical Sciences
10 PUBLICATIONS **17** CITATIONS
SEE PROFILE

Hamid Reza Khorram Khorshid
University of Social Welfare and Rehabilitation Sciences
85 PUBLICATIONS **434** CITATIONS
SEE PROFILE

Iran Red Crescent Med J. Inpress(Inpress): e21577. doi: 10.5812/ircmj.21577

Published online 2016 February 20. **Rapid Communication**

Contovir - A New Adjuvant Therapy in Recurrent Respiratory Papillomatosis: A Case Study

Mohammad Farhadi,[1] Farzad Izadi,[1,*] Maryam Bahri,[1] Vitta Derakhshandeh,[1] Mohammad Moein Tavakoli,[1] Hamid Reza Khorram Khorshid,[1] Hessamodin Madani,[1] Roya Shahrivar,[1] and Aslan Ahmadi[1]

[1]ENT-Head and Neck Surgery Research Center and Department, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, IR Iran

*Corresponding Author: Farzad Izadi, ENT-Head and Neck Surgery Research Center and Department, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, IR Iran. E-mail: farzadizadi@dr.com

Received 2014 July 5; **Revised** 2015 April 7; **Accepted** 2015 May 4.

Abstract

Background: Contovir is a mixture of herbal extracts (*Tanacetum vulgare, Rossa canina, Urtica dioica*) that is supplemented with selenium.
Objectives: This study aimed to add Contovir to the classic treatment of recurrent respiratory papillomatosis (RRP) in order to decrease the severity and extent of the disease, elongate the surgical intervals and improve the sense of patient well-being. Furthermore, we had to adjust the prescribed drug dosage, since there were no previous findings available.
Patients and Methods: This is a case study of RRP patients treated with Contovir as an adjuvant to the classic treatment, from March 2011 to February 2013, at an academic tertiary hospital (Rasoul-e-Akram hospital). All patients underwent surgical removal of papilloma and then were prescribed Contovir. Disease severity was quantified based on Derkay's staging system.
Results: Eight patients were enrolled in this study. The extent and severity of the disease improved in six cases. One had no response, and the severity of disease increased in one patient. Patients with supraglottic lesions had better responses to Contovir adjuvant therapy. No immediate or long-term side effects were reported.
Conclusions: Although Contovir has been found to be an advantageous adjuvant for RRP treatment, further studies are called for to verify these findings.

Keywords: Recurrent Respiratory Papillomatosis (RRP), Adjuvant Therapy, Contovir

1. Background

Recurrent respiratory papillomatosis (RRP) is a recurrent benign tumor of the respiratory tract. It is caused by genital tract human papillomaviruses (type 6 and 11 are the most common causes). This disease is transmitted during normal vaginal delivery from the infected birth canal to the respiratory tract of the child (1). The incidence of RRP in children is 1 - 4 per 100,000 and among adults is 1.8 - 3.9 per 100,000 (2). The major treatment modality for RRP is surgical de-bulking of papilloma by means of laser ablation or microdebridment. RRP does not cure the disease, due to papilloma regrowth after surgical removal. Studies have shown that approximately 4.4 procedures per year are needed for each patient with severe RRP (3). The frequent surgery requirement brings emotional and economic burdens on the patients and their families. Accordingly, laryngologists attempt to reduce the frequency of procedures by using non-invasive modalities including supplementation with an antiviral adjuvant. The criterion for adjuvant therapy is the need for surgery more than four times per year (4). Clinical trials have shown some controlling effect of adjuvants such as interferon alfa, cidofovir, indole-3-carbinol, acyclovir, ribavirin, isotretinoin, methotrexate, the mumps vaccine, and photodynamic therapy on RRP treatment. Interferon alfa and cidofovir have antiviral activities, and they also modulate the host immune response to HPV (4). Contovir, as a new version of an IMOD (immuno-modulatory drug), is a mixture of herbal extracts (*Tanacetum vulgare, Rossa canina, Urtica dioica*) supplemented with selenium, carotene and flavonoids (5, 6). The anti-inflammatory and antioxidative effects of IMODs have been shown on colitis, type 1 diabetes, pancreatic Langerhans islet transplantation and polycystic ovary syndrome. Previous studies showed the immunostimulation and antiviral effect of IMODs in HIV-infected patients (7, 8). Safety and potential mutagenic and genotoxic studies in the preclinical and clinical phase have demonstrated that IMODs are safe and non-mutagenic (6).

2. Objectives

Based on the requirement for a new, safe and cost-effective adjuvant, this study evaluates Contovir as a supplement to the classic treatment of RRP.

3. Patients and Methods

3.1. Methods

This is a case study regarding patients with RRP, which were enrolled in a prospective follow-up using Contovir for the treatment of RRP from March 2011 to February 2013 in Rasoul-e-Akram hospital; a tertiary referral hospital in Tehran, Iran affiliated with Iran University of Medical Sciences. Prior to beginning the treatment with Contovir, patients underwent endoscopic evaluation in the operating room to locate and quantify the extent of the disease. The rate of recurrence was determined by reviewing the last 12 months of surgical history. To standardize the treatment, the surgeon discontinued all other adjuvant therapies including I3C and INF.

Disease severity was quantified based on the staging system described by Derkay et al. (9) The initial dose of Contovir was 1.5 mg/kg IV. Since it causes phlebitis in children, it was administered orally. Contovir dosing was continued as: 3 mg/kg, 6 mg/kg (10_{th} study month), 20 g/kg (16_{th} study month).

3.2. Patients

Pretreatment laboratory tests were performed on all patients, including CBC diff, FBS, BUN, Cr, Na, K, liver function tests, and urinalysis. These tests were repeated before each surgery. Patients, or their parents, consented to the drug administration. In each surgery, the patient's voice and airway condition was documented. Patients were also asked about experienced side effects.

This study was approved by the institutional review board of Tehran University of Medical Sciences ethics committee. Written informed consent was obtained from the patients, and the study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki, as reflected in a prior approval by the institution's human research department.

4. Results

To evaluate the efficacy of Contovir in the treatment of RRP, nine patients were enrolled in this study. One patient dropped out during follow-up, due to noncompliance with the medication.

Demographic data for the patients are shown in Table 1. Average age at initial treatment of RRP was 3.6 years. Patients were between 2 and 56 years old. Seven patients were ≤ 15 years old. Case 1 had glottic stenosis secondary to malpractice and multiple surgeries for RRP in another center. Due to this patient's weak responses to surgery and the medication used in this trial, we had to administer INF and I3C, and after all four surgeries, his Derkay's scores were not changed.

This study included six patients who responded to Contovir as adjuvant therapy. The score remained constant for one patient (case 3) and was increased for another (case 1).

The response appeared after the second surgery on Contovir (P = 0.042) and two patients showed more significant response to Contovir (cases two and six).

In cases two and eight papilloma disappeared in the supraglottis, and in cases four and seven the lesion's extension decreased in the supraglottis. This change was more visible after the second surgery on Contovir. In addition, the glottic lesions responded on the third surgery.

Tracheal and subglottic papilloma did not respond to Contovir, demonstrating that only two of five patients with tracheal involvement had a decreasing tracheal score.

Table 1. The Patients' Scores at Initiation and After Contovir Treatment, the Subunits Score and the Extension and Severity of Papilloma

Subunits	Pre Contovir Score	1th OP on Contovir	2th	3th	4th	5th	6th	7th
Patient number =1; Gender = male; Age, y = 2; Age (First presentation), y = 0.5; Total Number of Opertion in Last Year = 5; Comorbidity = Glottic stenosis; Tracheotomy = +								
Supra glottis	22	21	6	21	12	24	6	21
Glottis	12	12	9	12	12	12	12	12
Sub glottis	3	3	3	3	3	3	3	3
Trachea	6	9	6	6	3	9	9	9
Total	43	45	24	42	30	48, (INF+I3C) 6	3020	45
Patient number =2; Gender = male; Age, y = 4; Age (First presentation), y = 1.5; Total Number of Opertion in Last Year = 4; Comorbidity = None; Tracheotomy = +								
Supra glottis	4	0	0	0				
Glottis	1	0	0	0				

Sub glottis	3	0	0	0			
Trachea	6	9	4	2			
Total	14	9	4	2[a]			
Patient number = 3; Gender = female; Age, y = 15; Age (First presentation), y = 5; Total Number of Opertion in Last Year = 4; Comorbidity = None; Tracheotomy = +							
Supra glottis	0	0	0	0			
Glottis	0	0	0	0			
Sub glottis	0	0	0	0			
Trachea	6	9	9	6			
Total	6	9	9	66			
Patient number = 4; Gender = male; Age, y = 11; Age (First presentation), y = 1; Total Number of Opertion in Last Year = 3; Comorbidity = None; Tracheotomy = -							
Supra glottis	6	3	6	1	3	6	3
Glottis	5	7	6	2	9	6	4
Sub glottis	0	0	1	0	1	3	0
Trachea	3	0	0	0	0	0	0
Total	14	10	13	3	13	15	7
Patient number = 5; Gender = male; Age, y = 56; Age (First presentation), y = 3; Total Number of Opertion in Last Year = 1; Comorbidity = None; Tracheotomy = -							
Supra glottis	0	3	3	0	0		
Glottis	6	3	3	1	0		
Sub glottis	3	3	3	3	3		
Trachea	6	3	3	6	9		
Total	15	12	12	10	12		
Patient number = 6; Gender = female; Age, y = 15; Age (First presentation), y = 13; Total Number of Opertion in Last Year = 4; Comorbidity = None; Tracheotomy = -							
Supra glottis	0	1	0				
Glottis	9	2	1				
Sub glottis	0	0	0				
Trachea	0	0	0				
Total	9	3	1				
Patient number = 7; Gender = female; Age, y = 3.5; Age (First presentation), y = 3.5; Total Number of Opertion in Last Year = 0; Comorbidity = GE reflux; Tracheotomy = -							
Supra glottis	6	6	0	2	2	0	0
Glottis	9	9	9	5	9	9	6
Sub glottis	0	0	0	0	0	0	0
Trachea	0	0	0	0	0	0	0
Total	15	15	9	7	11	9	6
Patient number = 8; Gender = female; Age, y = 9; Age (First presentation), y = 4; Total Number of Opertion in Last Year = 0; Comorbidity = None; Tracheotomy = -							
Supra glottis	3	0	0	1			
Glottis	9	9	9	8			
Sub glottis	0	0	0	0			
Trachea	0	0	0	0			
Total	12	9	9	9			

[a]During one year follow up, any lesion didn't see in laryngoscopy.

5. Discussion

Numerous studies have been designed to evaluate the role of different adjuvants for improvement of the course of RRP. Interferon alfa is the most common adjuvant therapy for RRP. In one study of 60 RRP patients, Leventhal et al. reported a 78% response rate to interferon (10). Rosen et al. showed, in a study of 21 RRP patients treated with indole-3-carbinol, a complete response in 33%, a partial response in 30% and no response in 37% of patients (11). In a review of the intra lesional effect of cidofovir on RRP patients by Chadha et al., patients demonstrated 57% complete resolution, 35% partial response and 8% no improvement (12).

Despite the positive responses to these medications, their adverse effects are mentioned. Neuropsychiatric complications and bone marrow suppression are two major complications of interferon. One of its limitations is a rebound phenomenon after a primary positive response (4). In addition, intravenous cidofovir has nephrotoxic side effects and it is potentially carcinogenic in animals (12).

In our study, six of eight patients responded to Contovir. It is not understood why some patients experienced near complete remission of papilloma, whereas others had partial responses or none at all. HPV11 and tracheal lesions are two predictors of severe RRP (13). Case 1 had laryngeal comorbidity, and this patient's HPV type was HPV11. Case 3 had only tracheal involvement. These are important characteristics to define the lack of response to Contovir. It is important to note that the response to Contovir was rapid and occurred after the second surgery.

Both cases 2 and 6, who had good responses, had four surgeries in the last year . These cases showed a decrease in disease scores on the supraglottis and glottis. They were followed for one year, and their score did not increase. Supraglottic and glottic lesions showed better and more significant responses compared to subglottic and tracheal papilloma. No adverse effect (clinical and laboratory) was detected in this study.

There are no previous studies of Contovir administration for treatment of RRP. Our findings provide beneficial evidence of Contovir as an adjuvant for RRP treatment that is efficacious, well-tolerated and a noninvasive oral drug. The limitations of the present study include lack of a control group, unknown HPV typing and short-term follow-up. Therefore, additional studies are recommended.

5.1. Conclusion

Our results show that Contovir can be a safe and effective adjuvant therapy for patients with RRP, but further clinical trials are necessary before it can be recommended for widespread use.

Footnotes

Authors' Contribution: All authors have contributed equally in all parts of the manuscript preparation process including: 1, study concept and design; 2, acquisition of data; 3, analysis and interpretation of data; 4, drafting of the manuscript; 5, critical revision of the manuscript for important intellectual content; 6, statistical analysis; 7, administrative, technical, and material support; 8, study supervision.

Funding/Support: Iran University of Medical Sciences.

References

1. Shah K, Kashima HK, Polk BF, Shah F, Abbey H, Abramson A. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstetrics & Gynecology.* 1986;**68**(6):795–9.
2. Bielecki I, Mniszek J, Cofala M. Intralesional injection of cidofovir for recurrent respiratory papillomatosis in children. *Int J Pediatr Otorhinolaryngol.* 2009;**73**(5):681–4. doi: 10.1016/j.ijporl.2009.01.002. [PubMed: 19193450]
3. Omland T, Lie KA, Akre H, Sandlie LE, Jebsen P, Sandvik L, et al. Recurrent respiratory papillomatosis: HPV genotypes and risk of high-grade laryngeal neoplasia. *PLoS One.* 2014;**9**(6):e99114. doi: 10.1371/journal.pone.0099114. [PubMed: 24918765]
4. Kimberlin DW. Current status of antiviral therapy for juvenile-onset recurrent respiratory papillomatosis. *Antiviral Res.* 2004;**63**(3):141–51. doi: 10.1016/j.antiviral.2004.06.013. [PubMed: 15451182]
5. Azonov JA, Khorshid HRK, Novitsky YA, Farhadi M, Ghorbanoghli Z, Shahhosseiny MH. Protective effects of setarud (IMODTM) on development of diet-induced hypercholesterolemia in rabbits. *Daru J Pharm. Sci.* 2008;**16**(4):218–22.
6. Khorshid HRK, Novitsky YA, Abdollahi M, Shahhosseiny MH, Sadeghi B, Madani H, et al. Studies on potential mutagenic and genotoxic activity of Setarud. *Daru J Pharm Sci.* 2008;**16**(4):223–8.
7. Rezvanfar MA, Rezvanfar MA, Ahmadi A, Shojaei-Saadi HA, Baeeri M, Abdollahi M. Molecular mechanisms of a novel selenium-based complementary medicine which confers protection against hyperandrogenism-induced polycystic ovary. *Theriogenology.* 2012;**78**(3):620–31. doi: 10.1016/j.theriogenology.2012.03.008. [PubMed: 22541319]
8. Baghaei A, Esmaily H, Abdolghaffari AH, Baeeri M, Gharibdoost F, Abdollahi M. Efficacy of Setarud (IMod), a novel drug with potent anti-toxic stress potential in rat inflammatory bowel disease and comparison with dexamethasone and infliximab. *Indian J Biochem Biophys.* 2010;**47**(4):219–26. [PubMed: 21174949]
9. Derkay CS, Malis DJ, Zalzal G, Wiatrak BJ, Kashima HK, Coltrera MD. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. *The Laryngoscope.* 1998;**108**(6):935–7.
10. Leventhal BG, Kashima HK, Mounts P, Thurmond L, Chapman S, Buckley S, et al. Long-term response of recurrent respiratory papillomatosis to treatment with lymphoblastoid interferon alfa-N1. Papilloma Study Group. *N Engl J Med.* 1991;**325**(9):613–7. doi: 10.1056/NEJM199108293250904. [PubMed: 1861694]
11. Rosen CA, Bryson PC. Indole-3-carbinol for recurrent respiratory papillomatosis: long-term results. *J Voice.* 2004;**18**(2):248–53. doi: 10.1016/j.jvoice.2003.05.005. [PubMed: 15193659]
12. Chadha NK, James AL. Antiviral agents for the treatment of recurrent respiratory papillomatosis: a systematic review of the English-language literature. *Otolaryngol Head Neck Surg.* 2007;**136**(6):863–9. doi: 10.1016/j.otohns.2006.09.007. [PubMed: 17547971]
13. Kayode A. The descriptive review, from recurrent respiratory papillomatosis of the disease, an enigmatic. *scielo.* 2012;**16**(1):108–14.